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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/036,208	10/29/2001	Hiroyuki Odaka	2530 US1P	4444

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EXAMINER	
ANDERSON, JAMES D	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 07/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/036,208	ODAKA ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,7,11 and 24-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,7,11 and 24-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2 sheets*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed May 17, 2006, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Status of the Claims

Claims 1, 4, 7, 11 and 24-27 are currently pending and are the subject of this Office Action. Claims 1, 4 and 11 are currently amended. Claims 2-3, 5-6, 8-10, 12-23 and 28-50 are cancelled.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 17, 2006 has been entered.

Election/Restrictions

The specie election requirement of a specific sensitizer and anorectic as required in the Office Action mailed September 4, 2002 is hereby withdrawn and all sensitizers and anorectics that fall within the scope of the instant claims are now under examination.

Claim Rejections - 35 USC § 112 – First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26 and 27 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the instant case, there is no written basis in the originally filed disclosure for the limitations "concomitantly" (instant claim 26) or "separately" (instant claim 27), which were added to the claims in the preliminary amendment filed on October 29, 2001. For applications filed before September 21, 2004, preliminary amendments are not part of the originally filed disclosure unless they are mentioned in the Oath or Declaration as originally filed. See MPEP 608.04(b). No mention of the October 29, 2001 preliminary amendment is in the Oath or Declaration as filed. Therefore, any added limitations in

such a preliminary amendment must have a written basis in the other papers as filed, such as the specification, abstract, claims, etc. to prevent a new matter issue. In the instant case, no support for the "concomitantly" and "separately" limitations is found in the originally filed disclosure.

Thus, claims 26 and 27 are rejected for adding subject matter not present in the application as originally filed.

Claim Rejections - 35 USC § 112 – Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4, 7, 11 and 24-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Independent claims 1, 7, and 25 recite the limitation "effective amount" in Line 3 of each respective claim. From the preamble of the claims, it is implied that the amount being administered is effective for lowering the concentration of glycosylated hemoglobin. However, this is only an implied limitation and is thus not clear and concise as required under 35 U.S.C. § 112, Second Paragraph.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The instant claims are drawn to a method of lowering glycosylated hemoglobin levels in mammals through the administration of an insulin sensitizer and an anorectic. In an effort to overcome rejections under U.S.C. § 103 detailed in the Final Office Action mailed December 5, 2005, applicants amended the instant claims to recite specific insulin sensitizers (pioglitazone and rosiglitazone). Support for this amendment is found in the instant specification on page 18, lines 35-36. Applicants have argued that the claimed sensitizer (rosiglitazone) is structurally similar to pioglitazone and is therefore included in the "(Pioglitazone and) structurally related insulin sensitizers" implicated for acceptance by Examiner Cook. (Applicant Arguments, page 7). This argument has been considered but is not deemed to be persuasive. The evidence of unexpected results (demonstrated in the 37 C.F.R. 1.132 Declaration of Dr. Okada) only supports the obviousness to the extent of the actual tested materials and is not inclusive of

similar materials or chemical structures without some evidence of "unexpected results" to support the extending of subject matter to similar materials or chemical structures. Said Declaration lacks any indication that the unexpected results disclosed therein can reasonably be extended to any other materials than those specifically tested as summarized in said Declaration (*i.e.* pioglitazone and sibutramine).

Claims 1, 4 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grossman *et al.* (Exp. Opin. Invest. Drugs, 1997, vol. 6, pp. 1025-1040) and Inoue *et al.* (Am. J. Clin. Nutr., 1992, v. 55, pp. 199S-202S) in view of WO 93/03724.

Grossman *et al.* review the mechanisms and clinical effects of thiazolidinediones in the treatment of diabetes mellitus. The insulin-sensitizer pioglitazone is disclosed as decreasing hyperglycaemia, hyperlipidaemia, hyperinsulinaemia and glucose intolerance in genetically obese and diabetic yellow KK mice and Zucker fatty rats (p. 1027, left column, first paragraph of Section 3.2). The clinical effects of the thiazolidinedione troglitazone demonstrated a significant decrease in HbA_{1c} supporting the concept that "thiazolidinediones can improve hyperglycaemia through decreased insulin resistance, as well as favourably influencing lipid metabolism" (p. 1032, second paragraph under Section 5.1.2). It is noted that the instant specification defines glycosylated hemoglobin as "HbA_{1c}" on page 32, line 33. The thiazolidinedione pioglitazone has been shown to reduce mean HbA_{1c} over 12 weeks in two Japanese dose-ranging studies (p. 1034, Table 4 and Figure 1). The reference does not disclose administration of pioglitazone and an anorectic in combination to reduce glycosylated hemoglobin.

Inoue *et al.* disclose that the anorexiant mazindol reduced food intake by directly suppressing neurons, inhibited gastric acid secretion, increased motor activity, decreased glucose absorption, and inhibited insulin secretion in obese patients (Abstract). The authors further suggest that "[I]t is worthwhile to use mazindol in the improvement of obesity-related diseases such as diabetes, hypertension, or hyperlipidemia" (p. 201S, last paragraph in "Conclusions").

The motivation to combine the references is found in WO 93/03724 wherein the authors state that, for the treatment of diabetes and disorders related to diabetes, what is needed is "a therapy that may be used in combination with anti-diabetic drugs to treat or prevent obesity, resulting from treatment with an insulin sensitizing drug or an insulin secretion stimulating drug" (p. 5, lines 9-11).

Thus, the present invention of lowering the level of glycosylated hemoglobin (HbA_{1c}) by administering a combination of an insulin-sensitizing agent (pioglitazone) and an anorectic (mazindol) would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Examiner notes that the instant method can be achieved with the instantly claimed insulin-sensitizing agent alone - the addition of an anorectic is not essential for the lowering of glycosylated hemoglobin.

Claims 1, 11, and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barman Belfour *et al.* (Drugs, 1999, v. 57, pp. 921-930) and Williams (Int. J. Obes., 1999, v. 23, Suppl. 7, S2-S4) in view of WO 93/03724.

Barman Belfour *et al.* disclose that the thiazolidinedione rosiglitazone is an antidiabetic agent that improves insulin resistance and decreases plasma glucose, insulin, and triglyceride levels (Abstract). It is further disclosed that rosiglitazone frequently increases food intake and promotes bodyweight gain in rats (p. 923, fourth bullet under the section "Effects on Glucose and Lipid Metabolism"). A randomized placebo-controlled study comparing rosiglitazone 4 and 8 mg/day, given as a single daily dose or in 2 divided doses, demonstrated that the drug decreased HbA_{1c} levels significantly (p. 925, left column, second bullet point; p. 926, Fig. 2). The reference does not disclose the administration of rosiglitazone and an anorectic in combination to reduce glycosylated hemoglobin.

However, Williams discloses that obesity is a major risk factor for the development of type 2 diabetes and is an important obstacle to the management of this disease (Abstract). Further, it is disclosed that conventional approaches to the management of type 2 diabetes that focus on glycaemic control often lead to weight gain (p. S3, first paragraph under section "Managing type 2 diabetes and obesity"). A potential solution to this apparent "conflct of interests" is suggested by Williams on page S3, first paragraph under the section "how to achieve and maintain weight loss" wherein he states that: "[I]t could be preferable to us[e] several different drugs to treat the individual disorders of this [diabetes] syndrome." As disclosed in the reference, clinical trials suggest that the use of the anorectic sibutramine could allow approximately one-third of patients with type 2 diabetes to achieve weight loss of at least 10% of their body

weight (p. S4, last paragraph). It is further disclosed that this weight loss would lead to a reduction in HbA_{1c} of up to 1% (p. S4, last paragraph).

The motivation to combine the references can be found in Williams as discussed *supra*. Further motivation is found in WO 93/03724 wherein the authors state that for the treatment of diabetes and disorders related to diabetes, what is needed is "a therapy that may be used in combination with anti-diabetic drugs to treat or prevent obesity, resulting from treatment with an insulin sensitizing drug or an insulin secretion stimulating drug" (p. 5, lines 9-11).

Thus, the present invention of lowering the level of glycosylated hemoglobin (HbA_{1c}) by administering a combination of an insulin-sensitizing agent (rosiglitazone) and an anorectic (sibutramine) would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

As discussed *supra*, the Declaration of March 7, 2003 by Dr. Odaka submitted under 37 C.F.R. 1.132 is only persuasive for a method of lowering the concentration of glycosylated hemoglobin in a mammal using the insulin sensitizer pioglitazone in combination with the anorectic sibutramine of claim 25 only.

Conclusion

Claims 1, 4, 7, 11 and 24-27 are rejected. Claim 25 is free of the prior art of record in view of the 37 C.F.R. 1.132 Declaration of Dr. Okada submitted March 7, 2003

demonstrating unexpected results with the specific combination of the insulin sensitizer pioglitazone and the anorectic sibutramine.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson
Examiner
Art Unit 1614

June 29, 2006

Ardin H. Marschel 7/8/06
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SUPERVISORY PATENT EXAMINER